Docket No.: 511582002421
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Aya JAKOBOVITS et al.

Application No.: 10/147,368

Filed: May 15, 2002

For: NUCLEIC ACIDS AND CORRESPONDING PROTEINS ENTITLED 101P3A11 OR PHOR-1 USEFUL IN TREATMENT AND DETECTION OF CANCER

Art Unit: 1642

Examiner: Minh-Tam B. Davis

DECLARATION OF DR. STEVEN B. KANNER

UNDER 37 C.F.R. § 1.132

Commissioner for Patents

Alexandria, VA 22313-1450

Dear Sir:

I, Steven B. Kanner, declare as follows:

1. I am Director, Cancer Research, at Agensys, the assignee of the present application. I am actively engaged in efforts to determine efficacy of antibody-based treatments for cancer. A copy of my current *curriculum vitae* is attached hereto as Exhibit A.

2. Along with my colleagues, I undertook an experiment to demonstrate the ability of antibodies immunoreactive with 101P3A11 v. 1 to inhibit the growth of tumors *in vivo* in mice. In these experiments, groups of SCID mice were injected subcutaneously with 2,000,000 prostate

cancer cells per mouse. There were five treatment groups with between 7-10 mice per group. Control groups received either PBS or KLH MAb, and test groups received either M3/47(3)24, a monoclonal antibody generated to the N-terminal peptide of 101P3A11 v. 1 containing amino acids 1-23 with an added linker (MVDPNGNESSATYFILIGLPGLESGSGC); M3/47(3)2, a monoclonal antibody raised against the N-terminal peptide of 101P3A11 v. 1 containing amino acids 1-23 with an added linker (MVDPNGNESSATYFILIGLPGLESGSGC); or M1/1G8, a monoclonal antibody generated against the Prostate Stem Cell Antigen. Treatment with antibodies started on the same day as tumor cell injection, and injections were repeated twice a week for a total of 12 doses of 250 μg administered IP. Tumor growth was followed over a period of 40 days.

3. The results are shown on the attached Exhibit B. As shown, after 40 days, the control group receiving PBS showed tumor volumes of almost 800 mm^3, while those provided MAb M3/47(3)24 showed tumor volumes of only 200 mm^3. The other monoclonal antibody directed to 101P3A11, M3/47(3)2, is less effective, but nevertheless slightly lower than at least the PBS control. It appears to have no statistical difference to the control KLH MAb. Two possible reasons that could account for the difference in efficacy between MAb M3/47(3)24 and its sister antibody M3/47(3)2 are: 1) differences in its epitope specificity and/or 2) its relative affinity for 101P3A11. Generally, monoclonal antibodies that are raised to the same antigen can differ in epitope specificity and relative affinity. Accordingly, these properties are unique to each antibody.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that

such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at Santa Monica, California on January 17, 2005.

Steven B. Kanner

STEVEN BRIAN KANNER, PH.D.

Agensys, Inc.
1545 17th Street
Santa Monica, CA 90404
Phone: 310.820.8029 (ext. 104)
Fax: 310.820.8489
E-mail: skanner@agensys.com

PROFILE

Pharmaceutical/Biotechnology research leader with extensive experience in novel target identification and validation, screen development and both small molecule drug and antibody discovery, with expertise in oncology, immunology and inflammation. Self-motivated strategic planner, skilled in motivating, developing, hiring, managing and building scientific teams to expedite novel drug/therapeutic candidate discovery for clinical trial consideration.

PROFESSIONAL EXPERIENCE

AGENSYS, INC. **2003 -**
Santa Monica, CA

Director, Cancer Research

Direct a research group including 19 scientists (Ph.D. and research associates) to identify, validate and develop novel targets for the generation of new therapeutics for cancer. Prioritize in-house portfolio for evaluation of targets for either monoclonal antibody development or for alliances for small molecule development or vaccine generation. Report to the Chief Scientific Officer.

- Establish teams for the validation of targets using RNAi knockdown technologies and over-expression systems to evaluate novel genes for establishing new monoclonal antibody based cancer therapies
- Serve on joint oversight committees with outside collaborators on alliances for propritetary targets to develop monoclonal antibodies, small molecule and vaccine approaches

BRISTOL-MYERS SQUIBB PHARMACEUTICAL RESEARCH INSTITUTE **1990 - 2003**
Princeton, NJ (in Seattle, WA from 1990-1997)

Associate Director, Immunology and Oncology Drug Discovery (1999 - 2003)

Directed a research group including 25 scientists (Ph.D. level and research associates) to identify, validate and develop novel targets for therapeutic intervention in both immunological/inflammatory diseases and cancer. Managed annual research budget for group ($250K) for laboratory operations, travel and training of scientific staff. Senior leader guiding the direction of the research effort in all pre-clinical drug discovery phases, including administrative functions, reporting to the Vice President of Immunology and Oncology Drug Discovery.

- Established a research group to identify novel targets for therapeutic intervention in both immunological/inflammatory diseases and cancer. Group developed reagents, assays, screens and analyses on over fifteen targets for future drug discovery projects
- Validated novel targets through bioinformatics, microarray technologies, Taqman for expression profiling, transgenic mouse development and analysis, flow cytometry, full-length cloning, monoclonal antibody generation and general protein expression/purification
- Generated eight new screening assays (enzymes, protein-protein interactions, receptor systems) in 1.5 years with reduced cycle time (3-6 month turnaround time) from target validation to screening campaign
- Transitioned an early-phase project on Itk kinase to full-phase status in 1999 (screening campaign, lead identification, followed by significant chemistry support for SAR), taking a small molecule inhibitor to preclinical animal model testing stages and identifying efficacious compounds
- In-licensed a project on p38 from an external partner at an early phase, then transitioned it to full-phase status (1999). Developed a small molecule drug candidate (2001) for IND toxicology and phase I study
- Developed a Src kinase project (1997-2000) in immunology before transitioning program to Oncology, with discovery of an optimized small molecule currently ready for phase I studies
- Co-chaired the Exelixis Oncology alliance, established to identify new targets for cancer. Nine new targets for oncology were identified in 1.5 years, and three high throughput assays were established
- Served on immunology/inflammation licensing team for identifying outside opportunities, and served on pulmonary licensing team and subcommittees for early-stage external technologies. Efforts led to the in-licensing of the p38 project and licenses for using inflammatory target technologies

Principal Scientist, Immunological Diseases (1997 - 1999)

Established a Signal Transduction group to identify small molecule therapeutics to treat immunological and inflammatory disorders. Group included 4 Ph.D. level investigators and 11 associate scientists involved in projects relating to targeting intracellular signaling components for identification of new drug candidates

Senior Research Investigator II, Immunodeficiency and Immunomodulation (1993 - 1997)
Seattle, WA (former Oncogen biotechnology company purchased by Bristol-Myers Squibb Company)

Senior Research Investigator I, Immunodeficiency and Immunomodulation (1990 - 1993)
Seattle, WA (former Oncogen biotechnology company purchased by Bristol-Myers Squibb Company)

UNIVERSITY OF VIRGINIA, DEPARTMENT OF MICROBIOLOGY AND CANCER CENTER **1986 - 1990**
Charlottesville, VA

Postdoctoral fellow, Oncology (advisor: J. Thomas Parsons, Ph.D.)

- Identified novel mechanisms of $p60^{src}$ activation in carcinogen-transformed embryonic cells
- Discovered novel tyrosine-phosphoyrlated substrates of the $p60^{src}$ oncogene by monoclonal antibody generation and biochemical characterization
- Commercialized monoclonal antibodies to FAK, tensin, $p120^{ctn}$, $pp60^{src}$, phosphotyrosine and cortactin

EDUCATION

Ph.D.	University of Miami (Immunology and Microbiology)	**1986**
B.A.	University of California, Berkeley (Genetics)	**1980**

HONORS, AWARDS, SCHOLARSHIPS AND FELLOWSHIPS

Bristol-Myers Squibb Excellence Awards	**1996 - 2002**
NIH Postdoctoral Fellowship Grant (F32-CA08316), University of Virginia	**1987 - 1990**
Presidential Scholarship, University of Miami	**1981 - 1986**
Honor Society, University of California, Berkeley	**1978 - 1980**

PROFESSIONAL AFFILIATIONS

American Association for Cancer Research
American Association of Immunologists
American Society for Microbiology
American Association for the Advancement of Science

AD HOC EDITORIAL ACTIVITY

Journal of Immunology
JI: Cutting Edge
Journal of Clinical Investigation
Journal of Biological Chemistry
Proc. Natl. Acad. Sci. USA
Molecular and Cellular Biology
Oncogene
Journal of Cellular Physiology
Antiviral Chemistry & Chemotherapy
Blood

SELECTED INVITED PRESENTATIONS

Regulated association between the SH3 domain of the Emt/Itk tyrosine kinase and multiple intracellular ligands. Lymphocyte Signal Transduction Workshop, Santorini, Greece (October, 2000)

Signal transduction through the T-lymphocyte receptors CD2 and LFA-1. Sugen, South San Francisco, California (June, 1996)

Lymphocyte antigen receptor activation of a novel FAK-related tyrosine kinase substrate. Lymphocyte Activation Meeting, Keystone Symposia on Molecular and Cellular Biology, Keystone, Colorado (April, 1994)

T-cell signaling via integrin receptors and immunoglobulin-superfamily molecules. University of Chicago, Committee on Immunology Seminar Series, Chicago, Illinois (March, 1994)

T-cell signaling through integrins and Ig superfamily receptors. Seattle Biomedical Research Institute, Seminar Series, Seattle, Washington (March, 1993)

β_2-integrin signaling in T-cells through PLCγ1 is TCR-dependent. Keystone Symposium on Phosphorylation/Dephosphorylation in Signal Transduction, Keystone, Colorado (January, 1993)

Regulation of TCR-induced PLCγ1 tyrosine phosphorylation by CD45. Plenary seminar at Biochemical Immunology Group Colloquium on the Structure and Function of the Leukocyte Common Antigen CD45, Edinburgh, Scotland (September, 1991)

PATENTS AND INVENTIONS

Raitano, A., S. B. Kanner, P. Challita, J. J. Perez-Villar, W. Ge, and A. Jakobovits. Nucleic acids and corresponding proteins entitled 158P3D2 useful in treatment and detection of cancer. November, 2004

Kanner, S. B., A. Raitano, P. Challita, J. J. Perez-Villar, W. Ge, and A. Jakobovits. Nucleic acids and corresponding proteins entitled 58P1D12 useful in treatment and detection of cancer. August, 2004

Raitano, A., P. Challita, J. J. Perez-Villar, W. Ge, S. B. Kanner and A. Jakobovits. Nucleic acids and corresponding proteins entitled 109P1D4 useful in treatment and detection of cancer. April, 2004

Barrish, J. C., J. Das, S. B. Kanner, C. Liu, S. H. Spergel, J. Wityak, A. M. P. Doweyko, and J. A. Furch. Thiazolyl inhibitors of Tec family tyrosine kinases. US6706717; March, 2004

Jakobovits, A., R. K. Morrison, A. B. Raitano, P. M. Challita-Eid, J. J. Perez-Villar, K. J. M. Morrison, M. Faris, W. Ge, , J. Gudas and S. B. Kanner. Nucleic acid and corresponding protein named 158P1D7 useful in the treatment and detection of bladder and other cancers. WO-04072263-A2; February, 2004

Kanner, S. B., A. Raitano, A. Jakobovits, P. Challita-Eid, W. Ge, J. J. Perez-Villar and M. Faris. Nucleic acids and corresponding proteins entitled 254P1D6B useful in treatment and detection of cancer. US-20040214212-A1; January, 2004

Perez-Villar, J. J., H. Chang, W-P. Yang, Y. Wu, G. S. Whitney and S. B. Kanner. Identification and cloning of a full-length human Clnk-related gene, MIST (Mast Cell Immunoreceptor Signal Transducer). US-020155563-A1; October, 2002

Chang, H., W-P. Yang, Y. Wu, G. S. Whitney, J. J. Perez-Villar and S. B. Kanner. Cloning and expression of human SLAP-2: a novel SH2/SH3 domain-containing human SLAP homologue having immune cell-specific expression. WO-0242457-A1; May, 2002

Kanner, S. B., A. B. Reynolds, S. J. Parsons and J. T. Parsons. Monoclonal antibodies to $p125^{FAK}$, $p120^{ctn}$, cortactin, $pp60^{src}$ and tensin. Licensed and commercialized from the University of Virginia to Upstate/Cell Signaling Solutions; 1991

Kanner, S. B., A. B. Reynolds and J. T. Parsons. Monoclonal antibody 6G9 to phosphotyrosine. Licensed and commercialized from the University of Virginia to Covance, Inc./Berkeley Antibody Company; 1991

PUBLICATIONS

1. Parks, W. P., G. B. Scott, **S. B. Kanner**, E. S. Hubbell, M. A. Fischl, G. M. Dickinson and E. R. Schiff. (1984) Acquired immunodeficiency syndrome and human T-cell leukemia virus in Miami: a household approach. *In* Human T-cell Leukemia Viruses (R. C. Gallo, M. Essex, and L. Gross, eds.), Cold Spring Harbor Press, New York. *pp.* 381-391

2. **Kanner, S. B.**, C. Cheng-Mayer, R. B. Geffin, W. P. Parks, G. A. Beltz, L. O. Arthur, K. P. Samuel and T. S. Papas. (1986) Human retroviral *env* and *gag* polypeptides: serologic assays to measure infection. *J. Immunol.* **137**:674-678

3. **Kanner, S. B.**, E. S. Parks, G. B. Scott and W. P. Parks. (1987) Simultaneous infections with human T cell leukemia virus type I and the human immunodeficiency virus. *J. Inf. Dis.* **155**:617-625

4. **Kanner, S. B.**, S. J. Parsons, J. T. Parsons and T. M. Gilmer. (1988) Activation of pp60$^{c\text{-}src}$ tyrosine kinase specific activity in tumor-derived Syrian hamster embryo cells. *Oncogene* **2**:327-335

5. Reynolds, A. B., D. J. Roesel, **S. B. Kanner** and J. T. Parsons. (1989) Transformation-specific tyrosine phosphorylation of a novel cellular protein in chicken cells expressing oncogenic variants of the avian cellular *src* gene. *Mol. Cell. Biol.* **9**:629-638

6. **Kanner, S. B.**, T. M. Gilmer, A. B. Reynolds and J. T. Parsons. (1989) Novel tyrosine phosphorylations accompany the activation of pp60$^{c\text{-}src}$ during chemical carcinogenesis. *Oncogene* **4**:295-300

7. **Kanner, S. B.**, A. B. Reynolds and J. T. Parsons. (1989) Immunoaffinity purification of tyrosine-phosphorylated cellular proteins. *J. Immunol. Methods* **120**:115-124

8. Reynolds, A. B., **S. B. Kanner**, H-C. R. Wang and J. T. Parsons. (1989) Stable association of activated pp60^{src} with two tyrosine-phosphorylated cellular proteins. *Mol. Cell. Biol.* **9**:3951-3958

9. Ely, C. M., K. M. Oddie, J. S. Litz, A. J. Rossomando, **S. B. Kanner**, T. W. Sturgill, and S. J. Parsons. (1990) A 42 kD tyrosine kinase substrate linked to chromaffin cell secretion exhibits an associated MAP kinase activity and is highly related to a 42 kD mitogen-stimulated protein in fibroblasts. *J. Cell Biol.* **110**:731-742

10. **Kanner, S. B.**, A. B. Reynolds, R. R. Vines and J. T. Parsons. (1990) Monoclonal antibodies to individual tyrosine-phosphorylated protein substrates of oncogene-encoded tyrosine kinases. *Proc. Natl. Acad. Sci. USA* **87**:3328-3332

11. **Kanner, S. B.**, A. B. Reynolds and J. T. Parsons. (1991) Tyrosine phosphorylation of a 120-kDa pp60^{src} substrate upon epidermal growth factor and platelet-derived growth factor receptor stimulation and in polyomavirus middle-T-antigen-transformed cells. *Mol. Cell. Biol.* **11**:713-720

12. Bouton, A. H., **S. B. Kanner**, R. R. Vines, H-C. R. Wang, J. B. Gibbs and J. T. Parsons. (1991) Transformation by pp60^{src} or stimulation of cells with epidermal growth factor induces the stable association of tyrosine phosphorylated cellular proteins with GTPase activating protein. *Mol. Cell. Biol.* **11**:945-953

13. Bouton, A. H., **S. B. Kanner**, R. R. Vines and J. T. Parsons. (1991) Tyrosine phosphorylation of three cellular proteins correlates with transformation of rat 1 cells by pp60^{src}. *Mol. Carcinogenesis* **4**:145-152

14. **Kanner, S. B.**, A. B. Reynolds, H-C. R. Wang, R. R. Vines and J. T. Parsons. (1991) The SH2 and SH3 domains of pp60^{src} direct stable association with tyrosine-phosphorylated proteins p130 and p110. *EMBO J.* **10**:1689-1698

15. Wu, H., A. B. Reynolds, **S. B. Kanner**, R. R. Vines and J. T. Parsons. (1991) Identification and characterization of a novel cytoskeleton-associated pp60^{src} substrate. *Mol. Cell. Biol.* **11**:5113-5124

16. Ledbetter, J. A., **S. B. Kanner**, G. L. Schieven and J. Deans. (1991) Transmembrane signals in T cells: tyrosine phosphorylation regulates phospholipase C activation. *In* Signaling Mechanisms in Secretory and Immune Cells (J. R. Martinez, B. S. Edwards and J. C. Seagrave, eds.), San Francisco Press, California. *pp.* 51-56

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27. Kavanagh, T. J., A. Grossmann, J. C. Jinneman, **S. B. Kanner**, C. C. White, D. L. Eaton, J. A. Ledbetter and P. S. Rabinovitch. (1993) The effect of 1-chloro-2, 4-dinitrobenzene exposure on antigen receptor (CD3)-stimulated transmembrane signal transduction in purified subsets of human peripheral blood lymphocytes. *Toxicol. Appl. Pharmacol.* **119**:91-99

28. Ledbetter, J. A., J. P. Deans, A. Aruffo, L. S. Grosmaire, **S. B. Kanner**, J. B. Bolen and G. L. Schieven. (1993) CD4, CD8 and the role of CD45 in T-cell activation. *Curr. Opin. Immunol.* **5**:334-340

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33. Parsons, M., J. A. Ledbetter, G. L. Schieven, A. E. Nel and **S. B. Kanner**. (1994) Developmental regulation of pp44/46, tyrosine-phosphorylated proteins associated with tyrosine/serine kinase activity in *Trypanosoma brucei*. *Mol. Biochem. Parasitol.* **63**:69-78

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37. **Kanner, S. B.**, A. Aruffo and P-Y. Chan. (1994) Lymphocyte antigen receptor activation of a focal adhesion kinase-related tyrosine kinase substrate. *Proc. Natl. Acad. Sci. USA* **91**:10484-10487

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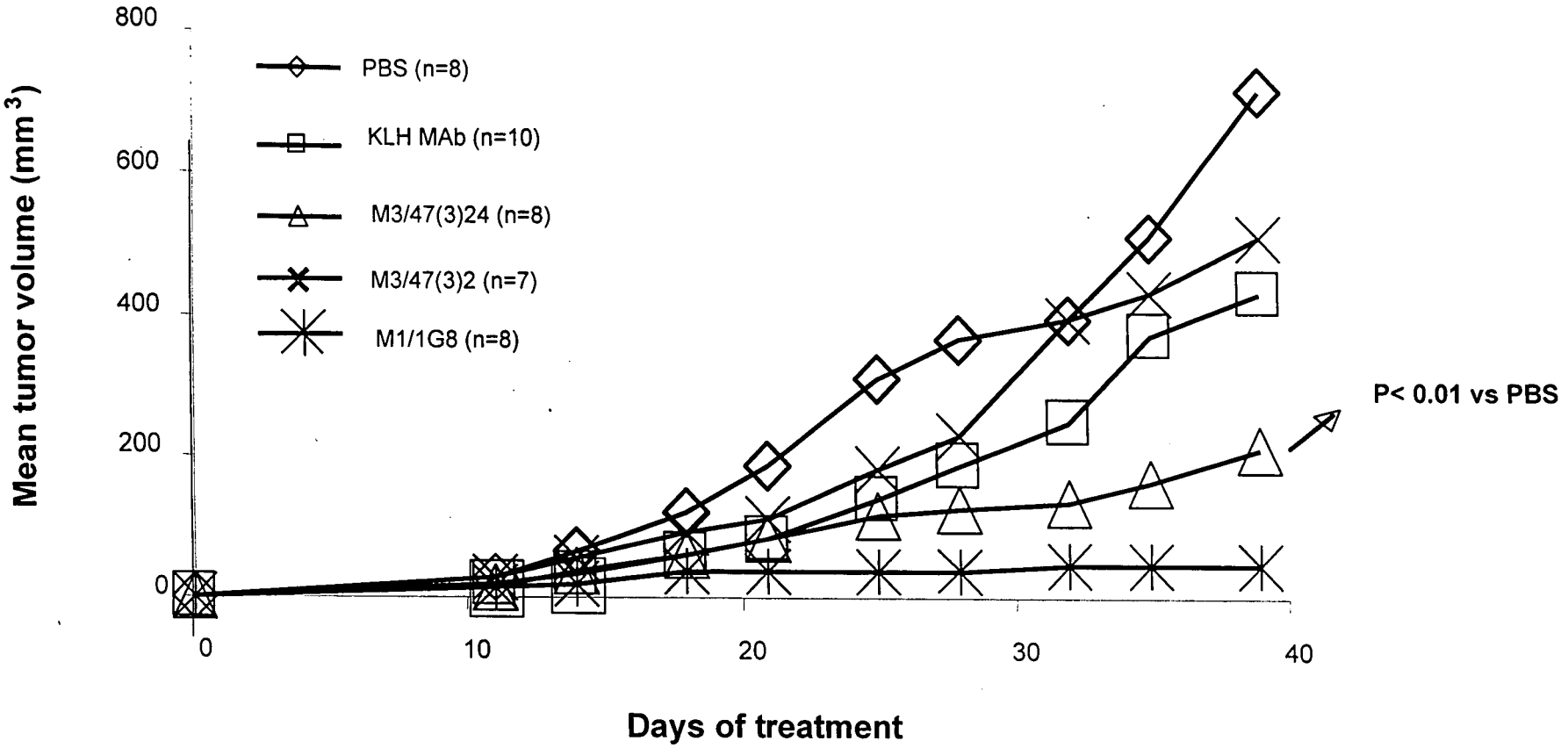
Exhibit B: PHOR-1 MAb M3/47(3)24 Inhibits Growth of Human Prostate Cancer Xenograft in Mice



- Treatment started on the same day of tumor cell injection (2 million/mouse) MAbs were dosed i.p. at 250 µg twice a week for a total of 12 doses.